REVIEW

Optimising the management of soft tissue tumours

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Summary

The Royal College of Pathologists of Australasia is developing a series of protocols as an educational tool to assist pathologists in the reporting of relevant information for specific cancer specimens. The protocol for the management of soft tissue tumour resections has recently been released, and this document elaborates the relevant literature on which that protocol drew. Sarcoma is uncommon but is associated with significant morbidity and mortality, and its management is complex. Diagnostic errors are not uncommon and these can have disastrous effects on patient outcome. Sophisticated ancillary testing is often an important adjunct to diagnosis and prognostication. Referral to a specialist sarcoma unit is indicated for both adult and paediatric sarcoma.

Key words: Multidisciplinary team, sarcoma, structured reporting.

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INTRODUCTION

The Royal College of Pathologists of Australasia (RCPA) is developing a series of protocols as an educational tool to assist pathologists in the reporting of relevant information for specific cancer specimens. Each protocol includes minimum requirements (termed 'standards' in the protocols) and recommendations ('guidelines'), to enhance the diagnosis and management of cancer across Australasia. The protocols also include aspects of multidisciplinary team (MDT) management, which forms the backbone of modern cancer care, and seek to provide advice to clinicians as to appropriate specimen handling and information exchange with other members of the MDT. The protocol for the management of soft tissue tumour resections¹ has recently been released, and this document summarises the major recommendations of that protocol, and reviews the pertinent literature. Where no specific references are given, the recommendations represent the expert opinion of the committee and their advisors. To some extent these protocols recapitulate similar documents developed in the United Kingdom and USA,^{2–5} but the RCPA project aims to be even more comprehensive and to tailor advice specifically to the circumstances of medical practice within Australasia.

The term sarcoma refers to a group of aggressive neoplasms composed primarily of cells arising from or differentiating towards mesenchymally derived tissues including bone, cartilage, fibrous tissue, nerve, muscle, blood and lymphatic vessels, and fat. Tumours arising in bone will be considered in a separate protocol; the remainder may be collectively termed 'soft tissue sarcoma' (STS). This group of tumours, whilst numerically uncommon, are clinically important, occurring at all ages and anatomic locations and resulting in significant morbidity, mortality and years of life lost. Collectively, STS constitutes some 1–2% of cancers but comprises more than 50 histotypes, so that individual sarcoma types range from uncommon to very rare. The collective 5-year survival for STS overall is estimated at around 50–60%² but within the group there is wide variation in clinical outcome, depending on patient age, tumour location and histotype.

The soft tissue tumour protocol addresses the preparation of structured reports for resections of soft tissue sarcoma and other soft tissue tumours with the potential for aggressive behaviour, such as those classified by the World Health Organization (WHO) as 'intermediate (locally aggressive)', e.g., desmoid type fibromatosis, well differentiated liposarcoma, or 'intermediate (rarely metastasising)', e.g., solitary fibrous tumour, angiomatoid fibrous histiocytoma.⁶ For convenience, these tumours are henceforth collectively referred to as sarcoma. Although it may be considered a sarcoma of the gastrointestinal tract, gastrointestinal stromal tumour (GIST) was not considered in the soft tissue protocol, as it displays a number of unique features (including different AJCC staging parameters)⁷ which warrant its separate consideration. Whilst cutaneous sarcoma may be managed outside the setting of a specialist sarcoma group, the relevant guidelines in this protocol should be applied to those lesions involving subcutis (e.g., a lesion recognised as atypical fibroxanthoma when confined to the dermis is likely to behave more aggressively if there is significant subcutaneous extension and/or vascular invasion,^{8,9} and may be more appropriately termed 'cutaneous pleomorphic sarcoma', with a comment regarding the possibility of aggressive behaviour, including some risk of distant metastasis). Cutaneous angiosarcoma also tends to behave aggressively and may require referral to a specialist unit.

Of note, the protocol may be applied to mesenchymal neoplasms arising not only in the extremities but at

intracavitary, head and neck, or visceral locations. Some modifications of the standard report may be required to include relevant information for selected sites (e.g., accurate assessment of margins may be difficult in sarcoma of the retroperitoneum, mediastinum or spermatic cord). In addition, many patients with soft tissue sarcoma (particularly paediatric patients) will be entered in clinical trials, and adherence to trial protocols may necessitate modifications or additions to the standard report. Because of the range of tumour types and sites in this group of cancers it is not feasible to develop specific protocols for each different histotype or anatomical location; rather, the committee have sought to provide a generic framework which can be adapted to individual cases, highlighting the major points of divergence from general rules (e.g., the differing grading systems for paediatric and adult sarcoma and some specific types such as rhabdomyosarcoma).

SOFT TISSUE SARCOMA IN AUSTRALASIA

Accurate figures for sarcoma incidence and mortality are difficult to obtain because of potential variations in coding: one would expect that soft tissue sarcomata would be coded under categories C47 and C49 but these are in fact likely to reflect mainly extremity tumours, whereas for example there is a separate category (C48) for tumours of the peritoneum and retroperitoneum, and it is reasonable to assume that at least some of these registrations (particularly in older males) will represent retroperitoneal sarcoma. Similarly, it is unclear whether uterine sarcoma will be classified under C49 or with other gynaecological cancers (C51–58), and so on. The most recent data (2005) show 536 new registrations in Australia¹⁰ for (C47 + C49) and a further 167 for C48. In New Zealand the registrations for the same period were 105 and 21, respectively.¹¹

No obvious aetiological agent is apparent in most cases, but a number of conditions (including Li-Fraumeni syndrome, hereditary retinoblastoma, neurofibromatosis and familial adenomatous polyposis) predispose some individuals to the development of sarcoma. Longstanding lymphoedema is associated with the development of lymphangiosarcoma and previous irradiation predisposes to angiosarcoma (classically in the breast), or post-radiation sarcoma not otherwise specified (NOS).

Histologically there are a number of benign mimics of sarcoma, including various benign neoplasms and reactive conditions, and diagnostic errors are not uncommon. Due to their relative rarity, widely varying clinical parameters, pathological complexity and multidisciplinary management needs, STS is best diagnosed and managed in the context of a specialist sarcoma centre, by healthcare professionals with specific interest and expertise in this area. Where a primary diagnosis of soft tissue sarcoma is made outside of this setting, the diagnosis should be reviewed by a pathologist with an interest in soft tissue pathology before definitive treatment is undertaken, and consideration should be given to referring the patient to a specialist unit for further management, even if primary excision has already been undertaken or attempted. A number of studies have shown that expert review will result in revised diagnoses in a significant number of cases (e.g., Thway and Fisher¹² found minor diagnostic discrepancies in 15.7% and major discrepancies in 10.9% of 349 specimens reviewed in a 12 month period). Similarly, there is evidence from several countries that patients treated in non-specialist centres, or whose referral to a specialist

centre is delayed, have worse outcomes including lower disease-free intervals and overall survival.^{13–15} Furthermore, at least in young patients, there is evidence that patients enrolled in clinical trials have consistently better survival than those not in trials.¹⁴ In some cases more than one MDT may need to be involved (e.g., the sarcoma team may consult with colleagues in gynaecology, urology, cardiothoracic or head and neck teams). All sarcomata ‘...should undergo definitive resection by a sarcoma MDT surgeon or by a surgeon with site-specific or age-appropriate skills, in consultation with the sarcoma MDT’.²

In soft tissue neoplasms, accurate diagnosis and tumour classification is the most important prognostic indicator, together with tumour stage and grade (which itself is dependent on histotype, as discussed below).^{16–18} Accurate histotyping not only allows prediction of clinical behaviour, but in the more aggressive tumours will guide management including the selection of patients for neoadjuvant or adjuvant chemo- or radiotherapy [e.g., the improved likelihood of response to ifosfamide in synovial sarcoma¹⁹ over other types, specific protocols for paediatric rhabdomyosarcoma or primitive neuroectodermal tumour (PNET), and so on], or the administration of targeted therapies for selected tumours (such as trabectedin for myxoid liposarcoma).²⁰ Prognostic information other than staging and grading may also be provided by careful pathological assessment (e.g., identifying myogenic differentiation in poorly differentiated pleomorphic sarcoma, discussed further below).

CLINICAL INFORMATION AND SURGICAL HANDLING

The first chapter of the protocol relates to information that should be collected, and procedures that are required, before handover of specimens to the laboratory. Some of this information (such as demographic information and patient identifiers) will be routinely collected for all pathology referrals, but additional specific information is required for accurate diagnosis and staging of sarcoma. In the case of resection specimens this includes the provision of sufficient information to localise the tumour bed for any subsequent therapy. Muscles and named blood vessels or nerves included in the resection should be clearly indicated, as well as other relevant landmarks (e.g., ‘groove at deep surface = dissected off brachial artery’), and this may be assisted by provision of a photograph or diagram.

For biopsy specimens the clinical diagnosis or differential diagnosis should be stated, as this improves clinicopathological correlation and promotes diagnostic accuracy, and any relevant imaging findings should be provided. Computed tomography (CT) or magnetic resonance imaging (MRI) appearances including depth and heterogeneity of the lesion, the presence of calcification, contrast enhancement, and attachment to or involvement of structures such as major nerves or blood vessels, can aid diagnosis. Ideally the imaging will be reviewed with the MDT pathologist prior to biopsy or resection being undertaken.

For resection specimens it must be stated if the patient has received neoadjuvant therapy, as extensive sampling of the specimen may be necessary to identify any residual viable tumour, which has prognostic significance,^{21–24} and it can be difficult to distinguish viable tumour macroscopically. Details of any previous biopsy diagnosis performed elsewhere, and any known sites of metastatic disease, should also be stated, as should a summary of the operative findings including tumour

extent (e.g., involvement of viscera, whether resected or not) and whether all visible tumour was resected. This forms an important parameter for staging⁷ and prognosis, and will guide decisions about further management such as adjuvant radiotherapy. Likewise, the specimen must be oriented in those cases where the status of specific surgical margins will determine the need for, or extent of, further surgery or radiotherapy. Close collaboration between surgeon and pathologist ensures accurate identification of relevant landmarks and close margins. This may be facilitated by direct handover of the specimen at the time of surgery (in the operating theatre or laboratory).

Wherever feasible, the specimen should be transported directly to the laboratory in its fresh state. This may be unnecessary if preoperative biopsy has rendered a confident diagnosis, but rapid transport to the laboratory may enable further ancillary studies (such as cytogenetic analysis), as well as harvesting of fresh tissue for tumour banking and allowing optimal fixation of tissue for possible electron microscopy. Wherever possible these decisions are best left to the pathologist in charge of the case.

SPECIMEN HANDLING AND MACROSCOPIC FINDINGS

This chapter relates to the procedures required after the specimen has been received in the laboratory. Pathologists may be asked to provide tissue samples from fresh specimens for tissue banking or research purposes. The decision to provide tissue should only be made when the pathologist is confident that the diagnostic process, including the assessment of the extent of tumour spread and other important parameters that influence patient prognosis and management, will not be compromised. As a safeguard, tissue taken for research purposes may be 'put on hold' until the diagnostic process is complete, so that this stored tissue can be retrieved if necessary. Consideration must be given to the likely differential diagnosis so that appropriate ancillary tests can be requested on fresh tissue (e.g., microbiological cultures, flow cytometry, cytogenetics, imprints for FISH, or fixation in glutaraldehyde for possible electron microscopy). Where employed, immediate harvesting of tissue for cytogenetics or imprints for fluorescence *in situ* hybridisation (FISH) should be undertaken upon receipt of the specimen.

Specific anatomical landmarks (such as major blood vessels, nerves, fascia or muscle bellies) should be identified prior to inking and incising the specimen. If there is doubt over the identification of such landmarks or specimen orientation, this should be clarified with the surgeon prior to proceeding. Where the specimen includes skeletal muscle, assessment of margins overlying the tumour will be unreliable once the muscle retracts after being cut and/or exposed to formalin and these margins should be measured prior to fixation. Most sarcoma resection specimens will be fairly large and will require a substantial volume of fixative, which may necessitate transferring the specimen to a larger container than that in which the specimen was transported.

Measurements of the specimen and of the tumour in three dimensions should be recorded wherever this is practicable. Tumour size is a necessary datum for staging, as is depth of the specimen with relation to deep fascia or intracavitary location.⁷ Therefore, the dissection and subsequent block selection should demonstrate the relationship of the tumour to the deep fascia where this is included in the specimen, and to other relevant

landmarks such as major nerves or blood vessels. The distance from the tumour to relevant surgical margins should be recorded, and the nature of the tissue between the tumour and the closest margin should be described (e.g., fat, muscle or fascia). A comment as to the nature of the tumour interface with normal tissue (e.g., infiltrative, well circumscribed or encapsulated) should also be offered. The appearance of the cut surface of the tumour should be described, noting areas of necrosis, haemorrhage or other variation in appearance, as these may reflect, for example, dedifferentiation or the presence of heterologous elements.

The presence and extent of necrosis should be noted and expressed as a percentage of the total tumour volume, as this will aid subsequent grading [where FNCLCC (Federation Nationale des Centres de Lutte Contre le Cancer) grading²⁵ is used; see later] or provide prognostic information in the event that neoadjuvant therapy has been administered. Specimen photography is a useful method of recording macroscopic appearances (described in more detail by Miettinen).²⁶ Adequate sampling of the tumour should be undertaken, with particular attention to areas which may have prognostic value (e.g., to confirm the presence of necrosis or to identify areas of varying differentiation, such as dedifferentiation in a well differentiated liposarcoma, or a round cell component in myxoid liposarcoma). In general, at least one block per centimetre of the maximum tumour diameter should be sampled, along with any previous biopsy tract or separate tumour nodules.

HISTOLOGY

The types of soft tissue specimen on which microscopy is performed include core biopsies, incisional and excisional biopsies, and larger resection specimens. Pre-operative core biopsy has a high diagnostic yield in skilled hands,^{27,28} and has largely replaced intraoperative frozen section, which is now rarely performed for sarcoma (and is generally not indicated to check surgical margins). The type of specimen submitted for histological examination has an important bearing on interpretation in terms of sampling error and security of the suggested diagnosis; e.g., a core biopsy from a small tumour may result in under-grading a sarcoma by missing areas of mitotic activity or necrosis, or areas of dedifferentiation, and limited sampling of stroma within a tumour may miss areas of specific differentiation and lead to a non-specific misdiagnosis, for example, spindle cell sarcoma of myofibroblastic type.

Resection will most often be performed following diagnosis by previous biopsy. If neoadjuvant therapy has not been undertaken, formal typing and grading may be performed on the resection specimen. Where applicable, grading should be performed using an accepted grading system, and this is addressed below. Some tumour types are definitionally regarded as either low or high grade, and for some (e.g., epithelioid sarcoma, clear cell sarcoma and alveolar soft part sarcoma) formal grading does not appear to correlate with prognosis.²⁹ If neoadjuvant therapy has been administered, the alteration in tumour morphology may preclude typing and grading, and reference to the previous biopsy material may be necessary (Fig. 1).

As mentioned earlier, accurate determination of tumour type is the most important prognostic predictor, and histotype must be identified before the most appropriate grading system can be applied. Accepting the limitations of sampling in biopsy specimens, wherever possible tumour type should be assigned according to the WHO classification.⁶ If precise tumour typing

Fig. 1 (A) Desmoplastic small round cell tumour, primary resection. (B) Metastasis from the same tumour, resected following adjuvant chemotherapy (H&E).

is not possible, generic descriptions of the tumour may be useful (e.g., myxoid, pleomorphic, spindle cell or round cell sarcoma), perhaps with a comment as to the perceived likelihood of aggressive behaviour.

Mitotic rate should be expressed as the number of mitoses per 10 high power fields (HPF), but counting should be performed in a greater number of fields (perhaps 50) as this may be quite variable throughout a tumour, and the presence of atypical forms should be noted. In some cases the presence or absence of mitoses may be an important factor to consider in arriving at a diagnosis at all (e.g., in a nerve sheath tumour with diffuse nuclear atypia and increased cellularity, the presence of mitoses may lead to a diagnosis of low grade malignant peripheral nerve sheath tumour rather than cellular neurofibroma with atypical features,³⁰ and the presence of more than very occasional mitoses in a differentiated smooth muscle neoplasm in deep soft tissue suggests smooth muscle tumour of uncertain malignant potential, rather than somatic leiomyoma).³¹ The presence and extent of necrosis should be documented, and care should be taken to distinguish between true tumour necrosis and simply stromal hyalinisation or infarction. Surgical margins should be measured histologically if under 2 cm, and the nature of the tissue constituting that margin (e.g., fascia/muscle/fat) should be documented, as a narrower surgical margin will be considered 'adequate' if that margin constitutes a tissue plane (such as fascia, joint capsule, tendon, epineurium, vascular sheath, cartilage, pleura or peritoneum) and 'inadequate' margins may affect survival.^{32,33}

Although most soft tissue tumours spread haematogenously, some notable exceptions (e.g., epithelioid sarcoma and synovial sarcoma) may spread via lymphatics, and any lymph nodes included in the specimen should be examined histologically. The presence or absence of vascular invasion and, where applicable, bone invasion, should be documented. Where neoadjuvant chemo- and/or radiotherapy has been administered, the residual tumour volume and degree of tumour regression/necrosis should be estimated, as this has independent prognostic value.^{21–24,33}

ANCILLARY STUDIES

Ancillary studies may be used to determine lineage, clonality or disease classification or subclassification; as prognostic biomarkers; or to indicate the likelihood of response to specific biological therapies. Immunohistochemistry plays a central role in sarcoma diagnosis; whilst typical examples of some tumour types (such as aggressive fibromatosis, well differentiated

liposarcoma or classical examples of biphasic synovial sarcoma) may be identified on the basis of morphology alone, immunohistochemistry will normally be employed to:

1. confirm an impression based on morphology;
2. distinguish between morphologically similar tumours;
3. support the diagnosis of rare tumour types;
4. support the diagnosis of a tumour arising in an unusual location or at an unusual age; and in some cases
5. provide prognostic information (e.g., Ki-67 index may enhance the predictive value of grading in some Grade 2 and 3 sarcomata).³⁴

Immunohistochemical markers may be employed to elucidate differentiation or lineage (e.g., SMA, desmin, h-caldesmon, myogenin, S-100 protein, CD31, EMA, various keratins) or to demonstrate protein expression as a surrogate for molecular events (e.g., ALK,^{35–37} MDM2 and CDK4,^{38–41} TFE3,^{42,43} INI-1,⁴⁴ TLE-1).^{45,46} In most instances the pattern of expression of a panel of these markers will serve to clarify the diagnosis (either to accurately classify the type of sarcoma, or to exclude alternative types of poorly differentiated tumour, such as metastatic carcinoma or melanoma). Furthermore, prognostic information may be gained in some cases, e.g., amplification of MDM2 without CDK4 in well differentiated/dedifferentiated liposarcoma portends a favourable prognosis;⁴¹ the presence of myogenic differentiation in otherwise unclassified pleomorphic sarcoma portends more aggressive behaviour than those which lack myogenic markers, signalling a worse overall prognosis and shorter time to metastasis^{47,48} (Fig. 2). Similarly, in rhabdomyosarcoma diffuse expression (defined as >80% of tumour cells) of myogenin (Myf4) appears to correlate with reduced relapse-free and overall survival, independent of translocation status, tumour site or stage.⁴⁹

A subset of soft tissue sarcomata have been found to harbour specific molecular genetic alterations which are characteristic of a particular histotype, and demonstration of these alterations through conventional karyotyping or molecular genetic analysis (such as FISH or PCR-based analysis with amplicon sequencing) may serve to confirm or refute a particular diagnosis, subclassify a tumour type or provide prognostic information (e.g., demonstration of CDK4 and MDM2 amplification in undifferentiated retroperitoneal sarcoma provides evidence that the tumour is in fact dedifferentiated liposarcoma).³⁹ Cytogenetic analysis will normally only be performed at source, as fresh tissue needs to be harvested and processed for cell culture at the time of resection. Karyotyping will not be

Fig. 2 Kaplan-Meier plots of metastasis rates in 88 soft tissue sarcomas of AJCC staging system (5th edition), stage II or III, originally diagnosed as MFH; 26 tumours showed myogenic differentiation and 62 did not ($p=0.006$). Reprinted from Fletcher *et al.*⁴⁷ © 2011 American Society of Clinical Oncology. All rights reserved.

helpful for every type of soft tissue tumour and may not be necessary if the diagnosis has already been established on biopsy material; however, if the diagnosis is uncertain and a cytogenetics service is available, it is prudent to harvest fresh material at the time of resection. This analysis may bring to light an unexpected diagnosis, or confirm the diagnosis in a tumour with non-classical histological appearances, arising in an unusual site or at an unusual age, or exhibiting an unusual immunophenotype.

These services are not always available but most specialist sarcoma units should at least have access to conventional karyotyping. Currently other forms of molecular testing such as PCR-based arrays and FISH are not reimbursed in Australia, but where these tests are not performed in-house they may be referred to other laboratories on a fee-for-service basis. It is to be hoped that this unsatisfactory situation may be resolved in the not-too-distant future, where such testing is necessary and appropriate to inform patient management. 'Commissioners should fund a formal system of second opinions and review of difficult cases, and molecular pathology and cytogenetics facilities.'²

Although in most instances diagnosis may be achieved through some combination of light microscopy, immunophenotyping, karyotyping and molecular genetic analysis, in a small number of cases ultrastructural examination may also prove helpful in elucidating a line of differentiation, e.g., to confirm the presence of endothelial or neural differentiation or to identify alternative lineages such as mesothelial or melanocytic differentiation. Again, this service is not available in all centres, and skilled interpretation of tumour ultrastructure is becoming a rarity amongst pathologists; however, in some cases this may provide useful adjunctive information.

Documentation of all relevant ancillary study findings is essential for final diagnostic synthesis, in which the significance of each finding is interpreted in the overall context of the case. This is particularly true in the case of molecular genetic testing; e.g., a FISH breakapart probe for EWSR1 may demonstrate rearrangement of that gene, but this molecular event can occur in several different tumours including PNET, desmoplastic small round cell tumour, angiomatoid fibrous histiocytoma, clear cell sarcoma, extraskeletal myxoid chondrosarcoma, a subset of myxoid liposarcoma, and a subset of

myoepithelial tumours,^{50–52} so that this information must be interpreted in the context of clinical information, morphology and immunophenotype.

SYNTHESIS AND OVERVIEW

Synthesis refers to the amalgamation of numerous pieces of information into a coherent, overarching commentary including diagnosis and prognostic parameters which are likely to form part of the report summary or 'diagnosis' field in the final pathology report. This will include elements such as tumour stage and grade, which will be arrived at through consideration of numerous factors discussed above (such as tumour size, depth, histotype, mitotic rate, the presence of necrosis and the results of ancillary testing).¹

In general, the RCPA recommends the use of the American Joint Committee on Cancer (AJCC) staging system⁷ for all solid tumours. But there are limitations in applying a system based on 'TNM' parameters when nodal metastases are rare in most types of STS; this tends to dichotomise the staging into those tumours with or without distant metastases, but is less helpful in stratifying localised primary tumours. However, the current system still has some prognostic value, and does provide a standardised system for consistent data collection and benchmarking.

Multiple grading systems and modifications thereof^{25,53–64} have been proposed for soft tissue sarcoma, dating from as early as 1927.⁵⁴ Some of these were developed with reference to a specific sarcoma type^{53–56,58,63} or age group,⁶² whereas others^{57,59–61,64} were intended for more general application. Regardless, many of these proposals have distinct limitations, and no one system is equally useful in all situations. However, at least in adult sarcoma, many experts advocate use of the FNCLCC system^{25,61} where it is applicable (Table 1). Although this system is not applicable to all sarcoma types, it is relatively easy to learn, is widely employed and has been shown to have better interobserver reproducibility than some other systems.⁶⁵ When applied appropriately, this system has prognostic value and predicts metastasis-free survival^{66,67} (Fig. 3). It also forms part of the current AJCC staging parameters⁷ and therefore is necessary for allocation of stage. For a more detailed description of the various systems proposed, the reader is referred to Kilpatrick's review.²⁹

Histotyping should be performed before any attempt at grading, and grading should not be used on 'intermediate malignancy' tumours. Furthermore, some histotypes (e.g., PNET, desmoplastic small round cell tumour) are definitionally regarded as high grade on the basis of their natural history, regardless of the results of formal grading.^{25,61,66} In cases where FNCLCC does not apply, a comment should be offered to this effect: e.g., 'desmoplastic small round cell tumour, definitionally high grade' or 'high grade pleomorphic sarcoma, not otherwise classified'.

In paediatric tumours, the situation is even more complicated, with separate systems for rhabdomyosarcoma and non-rhabdomyosarcomatous sarcoma other than the Ewing's family of tumours, which are definitionally regarded as high grade. In Australasia the Intergroup Rhabdomyosarcoma Study grouping^{63,68,69} is preferred for rhabdomyosarcoma, and the Children's Oncology Group (COG) grading⁶² for the 'non-rhabdomyosarcoma' group. Numerous studies have verified the prognostic value of this grading system, which is also used to devise treatment strategies. Tumour site should also be stated, as this also has prognostic significance (e.g., parameningeal rhabdomyosarcoma is definitionally considered to be high risk), and PAX fusion type also has prognostic significance⁷⁰

Table 1 FNCLCC grading system

Tumour differentiation	
Score 1	Sarcomas closely resembling normal adult mesenchymal tissue (e.g., well differentiated liposarcoma, well differentiated fibrosarcoma, well differentiated leiomyosarcoma, well differentiated chondrosarcoma)
Score 2	Sarcomas for which histological typing is certain (e.g., myxoid liposarcoma, conventional fibrosarcoma, myxofibrosarcoma, pleomorphic MFH with storiform pattern, conventional leiomyosarcoma, conventional angiosarcoma, myxoid chondrosarcoma)
Score 3	Embryonal and undifferentiated sarcomas, and sarcomas of doubtful type (e.g., round cell liposarcoma, pleomorphic liposarcoma, malignant peripheral nerve sheath tumour, pleomorphic MFH without storiform pattern, giant cell MFH, poorly differentiated/pleomorphic/epithelioid leiomyosarcoma, rhabdomyosarcoma, mesenchymal chondrosarcoma, extraskeletal osteosarcoma, synovial sarcoma, epithelioid angiosarcoma, undifferentiated sarcoma)
Mitotic count	
Score 1	0–9 mitoses per 10 HPF*
Score 2	10–19 mitoses per 10 HPF
Score 3	≥20 mitoses per 10 HPF
Tumour necrosis	
Score 0	No necrosis
Score 1	<50% tumour necrosis
Score 2	≥50% tumour necrosis
Histological grade	
Grade 1	Total score 2, 3
Grade 2	Total score 4, 5
Grade 3	Total score 6, 7, 8

Based on Trojani *et al.*,²⁵ Kilpatrick,²⁹ and Guillou *et al.*⁶¹

FNCLCC, Federation Nationale des Centres de Lutte Contre le Cancer; HPF, high power field; MFH, malignant fibrous histiocytoma.

Fig. 3 Metastasis-free survival in MFH (349 patients) according to histological grade. Grade 1 (33 patients), Grade 2 (160 patients), Grade 3 (156 patients). Reprinted from Coindre *et al.*⁶⁷ with permission from John Wiley and Sons.

and should be recorded. At any rate, these cases will most appropriately be managed in a specialist paediatric oncology unit, by a team familiar with the complexities of this area.

If a sarcoma has been resected outside a specialist unit or without consultation with a sarcoma MDT, the final diagnosis should be reviewed by a specialist soft tissue pathologist. As discussed in the preamble, there is good evidence that diagnostic errors are not uncommon and these discrepancies may have significant implications for clinical management and prognosis. Specialist management of this at times confusing but ultimately fascinating group of rare tumours will ensure the best possible outcome for the patient.

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